D. N.

AADA 64-104

JUL 2 1997

Fujian Institute of Microbiology
U.S. Agent: ChemWerth, Inc.
Attention: David R. Loomis
85 Rimmon Road
Woodbridge, CT 06525

Dear Sir:

This is in reference to your abbreviated antibiotic application dated September 15, 1993, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act, for Cyclosporine, USP (non-sterile bulk).

Reference is also made to your amendments dated March 14, April 7, and April 29, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is acceptable for manufacturing, processing or repacking, as defined in this application. Accordingly, the application is approved.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMIST'S REVIEW NO. #4

2. AADA #64-104

3. NAME AND ADDRESS OF APPLICANT
Fujian Institute of Microbiology (China)
U.S. Agent: ChemWerth, Inc.
Attention: David R. Loomis
85 Rimmon road
Woodbridge, CT 06525

Phone: 203-387-7794

4. LEGAL BASIS FOR SUBMISSION
21 CFR §448.23

Reference drug: Sandimmune® by Sandoz
(NDA #50-574, approved 11/14/83 for Oral Solution and Injectable)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME

Cyclosporine, USP (non-sterile bulk)

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Original application: 9/15/93
"Refuse to File" letter 10/12/93
Amend 1/7/94
"Refuse to File" letter 1/28/94
Amend 3/31/94
"Acknowledge" letter 4/20/94
N/A letter (Major) 7/26/94 by E.Duffy (a global review; microbial source unacceptable)
OGD letter 5/15/95 by D.Sporn
Amend 12/20/95
Amend 9/20/96 to N/A letter 7/1/96 (MAJOR)
Amend 12/5/96 to N/A letter 10/31/96 (MAJOR)
Amend 3/14/97 to N/A letter 3/6/97 (MINOR)
Amend 4/7/97 (Telephone amendment)
Amend 4/29/97 (Telephone amendment)

10. PHARMACOLOGICAL CATEGORY
Peptide antibiotic; Immunosuppressant

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
None cited

13. DOSAGE FORM
Non-sterile bulk

14. POTENCY
98.5-101.5% (anhydrous)

15. CHEMICAL NAME AND STRUCTURE
See CR #1

16. RECORDS AND REPORTS
N/A

17. COMMENTS

Since Firm uses a different microorganism to produce the drug substance [Current regulation under 21 CFR §430.4 (a)(51): "(51) *Cyclosporine*. Cyclosporine is a specific cyclic polypeptide consisting of 11 amino acids produced by the growth of *Cyclindrocarpon lucidum* Booth or *Tolypocladium inflatum* Gams."], in our letter 5/15/95 we ask Firm to propose a revision, and to submit supporting data which demonstrate the equivalence of the drug substance produced by them and that produced by Sandoz. Particular attention should be focused on the impurities present. If there are no differences, qualitatively or quantitatively, there should be no new safety of efficacy concerns.

In their original submission dated 9/15/93 (page 153), Firm submits results of degradation studies (pH and heat).

In Amendment 12/20/95:

Firm proposes to revise to: "(51) *Cyclosporine*. Cyclosporine is a specific cyclic polypeptide consisting of 11 amino acids produced by the growth of *Cyclindrocarpon lucidum* Booth or *Tolypocladium inflatum* Gams, and each of the same substances produced by any other means, is a kind of cyclosporine."

In Amendment 3/14/97 Firm responds to N/A letter in order:

Q1. It is recommended that "Manufacture Date" and "Expiration Date" be included in the Certificate of Analysis. What does it mean by "Reported Date" (Exhibit 1)?

A1. Firm agrees to do so. A template for the new COA

attached in Exhibit 1 is acceptable.

Q2. Please submit additional long-term stability data derived from all three batches (#960201, #951201 and #951101).

A2. The additional stability data (12 month for #951201, 9 month for #960201 and 6 month for #951101) included are acceptable.

Comments:

Firm needs to submit additional RT stability data for the three new batches to support the proposed 24 month expiration **dating, since no accelerated data for these three batches have ever been submitted.**

Because this application is the first generic version and FIM uses a different microorganism to produce the drug substance, we need to scrutinize this product more carefully. We telephoned the U.S. Agent ChemWerth (see memo dated 4/2/97) and two options are presented to Firm: 1) Start accelerated studies and submit 3 month data; or 2) Submit additional RT data from the three batches. If they submit 12 month RT data for the most recent batch (#951101, with 6 month data collected 1/15/97), we can grant a 12 month expiry dating. Firm may file supplements to extend their expiration dating when more data are generated.

In Telephone Amendment 4/7/97 Firm submits three month accelerated stability data (samples placed in the accelerated program on 7/15/96). All data meet specifications.

In Telephone Amendment 4/29/97 Firm includes revised COA for batch #951101. The values for have been verified by the QC Department who confirmed the calculation error. Stability results to date on the drug substance by the manufacturer have not shown any additional peaks other than the component peak and minor related compounds. Firm reports as "Not Detected" under "Degradation Products" in the submitted stability data reports.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval recommended

19. REVIEWER: Maria C. Shih
DATE COMPLETED: 4/29/97

1. CHEMIST'S REVIEW NO. #3

2. AADA #64-104

3. NAME AND ADDRESS OF APPLICANT
Fujian Institute of Microbiology (China)
U.S. Agent: ChemWerth, Inc.
Attention: David R. Loomis
85 Rimmon road
Woodbridge, CT 06525

Phone: 203-387-7794

4. LEGAL BASIS FOR SUBMISSION
21 CFR §448.23

Reference drug: Sandimmune® by Sandoz
(NDA #50-574, approved 11/14/83 for Oral Solution and Injectable)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Cyclosporine USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Original application: 9/15/93
"Refuse to File" letter 10/12/93
Amend 1/7/94
"Refuse to File" letter 1/28/94
Amend 3/31/94
"Acknowledge" letter 4/20/94
N/A letter (Major) 7/26/94 by E.Duffy (a global review; microbial source unacceptable)
OGD letter 5/15/95 by D.Sporn
Amend 12/20/95
Amend 9/20/96 to N/A letter 7/1/96
Amend 12/5/96 to N/A letter 10/31/96

10. PHARMACOLOGICAL CATEGORY
Peptide antibiotic; Immunosuppressant

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
None cited

13. DOSAGE FORM
Non-sterile bulk

14. POTENCY
N/A

15. CHEMICAL NAME AND STRUCTURE
See CR #1

16. RECORDS AND REPORTS
N/A

17. COMMENTS

Since Firm uses a different microorganism to produce the drug substance [Current regulation under 21 CFR §430.4 (a)(51): "(51) *Cyclosporine.* Cyclosporine is a specific cyclic polypeptide consisting of 11 amino acids produced by the growth of *Cyclindrocarpon lucidum* Booth or *Tolypocladium inflatum* Gams."], in our letter 5/15/95 we ask Firm to propose a revision, and to submit supporting data which demonstrate the equivalence of the drug substance produced by them and that produced by Sandoz. Particular attention should be focused on the impurities present. If there are no differences, qualitatively or quantitatively, there should be no new safety of efficacy concerns.

In Amendment 12/20/95:

Firm proposes to revise to: "(51) *Cyclosporine.* Cyclosporine is a specific cyclic polypeptide consisting of 11 amino acids produced by the growth of *Cyclindrocarpon lucidum* Booth or *Tolypocladium inflatum* Gams, and each of the same substances produced by any other means, is a kind of cyclosporine."

In Amendment 12/5/96 Firm responds to N/A letter in order:

Q1. Data have been submitted for only two exhibit batches, whereas we require data from three separate fermentations. Therefore, please manufacture another production batch and submit all performance data (i.e., COA, batch records and stability data) for our review.

A1. A third exhibit batch (#951101) was manufactured (see Table below). COA and the complete batch record is enclosed.

Comments:
Recommend Firm to include ▒Manufacture Date▒ and ▒Expiration Date▒ in the COAs.

Q2. Please specify the size of your typical production batches.

A2. The size of a typical production batch is based upon the processing of of crude product. Typical finished product batch sizes from the purification of this quantity of crude Cyclosporine is approximately

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Q3. It is noted from the executed batch records that prior each crude batch was analyzed for cyclosporine concentration and Is there a minimum limit of the latter for this in-process control? Please clarify.

A3. Firm states that the percentage of varies depending on the fermentation volume. Based on the current manufacturing process, the in-process specification established for this analysis is

Q4. Please submit additional available stability data derived from batches #960201 and #951201.

A4. Additional RT stability data for two batches (#960201 and #951201) up to 9 months and 3 months data for lot #951101 are provided. Data meet specifications.

Comments:

Since this is a first generic product, and Firm uses different microorganism to produce the drug substance, we need to scrutinize this drug product more carefully. In this letter we request samples for validation and request additional RT stability data for these three batches.

Q5. Regarding the final printed labels:

A. Please revise to "light-**resistant** containers".

B. We recommend you use "controlled room temperature" under "Storage".

C. Revise accordingly and submit **actual** specimens of your labels.

A5. The revised FPL submitted is OK.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable (MINOR)

19. REVIEWER: Maria C. Shih

DATE COMPLETED: 2/13/97

AADA 64-104

Fujian Institute of Microbiology
U.S. Agent: ChemWerth, Inc.
Attention: David R. Loomis
85 Rimmon Road
Woodbridge, CT 06525

Dear Sir:

This is in reference to your abbreviated antibiotic application dated September 15, 1993, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act, for Cyclosporine USP (non-sterile bulk).

Reference is also made to your amendment dated September 20, 1996.

The application is deficient and, therefore, not approvable under Section 507 of the Act for the following reasons:

1. Data have been submitted for only two exhibit batches, whereas we require data from three separate fermentations. Therefore, please manufacture another production batch and submit all performance data (i.e., COA, batch records and stability data) for our review.

2. Please specifiy the size of your typical production batches.

3. It is noted from the executed batch records that prior each crude batch was analyzed for cyclosporine concentration and
Is there a minimum limit of the latter for this in-process control? Please clarify.

4. Please submit additional available stability data derived from batches #960201 and #951201.

5. Regarding the final printed labels:

   A. Please revise to light-**resistant** containers .

   B. We recommend you use " controlled room temperature " under Storage .

   C. Revise accordingly and submit **actual** specimens of your labels.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

We are withholding the request for exhibit samples, until a third exhibit batch can be manufactured and all performance data reviewed satisfactorily.

We note that this letter represents the third occasion upon which significant (MAJOR) chemistry, manufacturing, and/or controls deficiencies have been identified which have precluded approval of your application(s). In an effort to facilitate the resolution of these deficiencies, we encourage you to contact Bob West (Project Manager) at (301) 594-0360, for further clarification or assistance in providing a satisfactory response to each of the deficiencies.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMIST'S REVIEW NO. #2

2. AADA #64-104

3. NAME AND ADDRESS OF APPLICANT
Fujian Institute of Microbiology (China)
U.S. Agent: ChemWerth, Inc.
Attention: David R. Loomis
85 Rimmon road
Woodbridge, CT 06525

Phone: 203-387-7794

4. LEGAL BASIS FOR SUBMISSION
21 CFR §448.23

Reference drug: Sandimmune® by Sandoz
(NDA #50-574, approved 11/14/83 for Oral Solution and Injectable)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Cyclosporine USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Original application: 9/15/93
"Refuse to File" letter 10/12/93
Amend 1/7/94
"Refuse to File" letter 1/28/94
Amend 3/31/94
"Acknowledge" letter 4/20/94
N/A letter (Major) 7/26/94 by E.Duffy (a global review; microbial source unacceptable)
OGD letter 5/15/95 by D.Sporn
Amend 12/20/95
Amend 9/20/96 to N/A letter 7/1/96

10. PHARMACOLOGICAL CATEGORY
Peptide antibiotic; Immunosuppressant

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
None cited

13. DOSAGE FORM
Non-sterile bulk

14. POTENCY
N/A

15. CHEMICAL NAME AND STRUCTURE
See CR #1

16. RECORDS AND REPORTS
N/A

17. COMMENTS

Since Firm uses a different microorganism to produce the drug substance [Current regulation under 21 CFR §430.4 (a) (51): "(51) *Cyclosporine*. Cyclosporine is a specific cyclic polypeptide consisting of 11 amino acids produced by the growth of *Cyclindrocarpon lucidum* Booth or *Tolypocladium inflatum* Gams."], in our letter 5/15/95 we ask Firm to propose a revision, and to submit supporting data which demonstrate the equivalence of the drug substance produced by them and that produced by Sandoz. Particular attention should be focused on the impurities present. If there are no differences, qualitatively or quantitatively, there should be no new safety of efficacy concerns.

In Amendment 12/20/95:

Firm proposes to revise to: "(51) *Cyclosporine*. Cyclosporine is a specific cyclic polypeptide consisting of 11 amino acids produced by the growth of *Cyclindrocarpon lucidum* Booth or *Tolypocladium inflatum* Gams, and each of the same substances produced by any other means, is a kind of cyclosporine."

In Amendment 9/20/96 Firm responds to N/A letter in order:

Q1. For Characterization of Cyclosporine produced by fermentation of Fusarium solani, we note
are very different among the three laboratories findings. It appears that they did not all use the methodology described on page 26 of your Amendment dated December 20, 1995. Please clarify. The individual from and pharmaceuticals should be provided.

A1. Firm states that they use the as published in USP. Differences in the as performed by the various laboratories may have resulted from variations in the testing equipment and slight modifications in the methodology as allowed for in system suitability. The methods and equipment used by the various laboratories are summarized (page 1). The differences between the and Firm's results

may be a result of slight differences in

may be to give more efficient but only rarely are they used at temperatures above because of potential The USP requires this assay to be run at which may lead to significant variations. Firm has enclosed the test methods but methodology from is not available.

Q2. Please discuss the type of Water used in the culture media, and provide specification and testing procedures for its QC assurance.

A2. Firm states that distilled water is used in the preparation of all culture media and throughout the purification process. Specifications and test methods are included.

Since the culture media that uses this water is subsequently sterilized, water that is used in this portion of the process is tested once or once every fermentation batches. Distilled water that is used in other areas of the process is tested at a frequency of This testing interval is based upon the water monitoring program that was initiated after the initial validation of the water system where

Q3. Please submit copies of final printed labels for this finished bulk product.

A3. The resubmitted labels included in Exhibit 2 are zeroxed copies. Words under "Storage" have been changed (see under **Comments** under #32 LABELING). **Ask Firm for actual specimen of FPL after revision.**

Q4. It is recommended that you translate the executed batch records completely. Such as the "Fermentation Batch Record" on page 213. All comments and results should be translated into English. Please do so for future submissions.

A4. Firm will ensure that all future submissions are fully translated.

Q5. Regarding the specifications for the finished bulk, please update your potency limit for cyclosporine to current USP standard (98.5 to 101.5%). We recommend "Appearance" be added as one of the testing items.

A5. The updated specifications including "Appearance" for the finished bulk drug enclosed in Exhibit 3 is acceptable. See under #28.

Q6. It is noted that the submitted COAs contain only the first four testing items of the seven listed on your specification sheet on page 112. Please clarify when you will analyze and report the remaining three items.

A6. Firm states that the remaining determinations for the exhibit batches,

were performed at the same time as the other test items. This information was inadvertently excluded from the submission since these tests results were issued on a separate COA. The September 15, 1993 submission contained the domestic market analytical determinations for this product and failed to include all of the USP test items. COAs for these batches containing the remaining results are enclosed (pp. 11-3).

In regard to the post-approval stability protocol:

Q7A. Please revise to the following:

The first three marketable production lots of the product should be placed on stability. Yearly thereafter, one production batch should be added to the stability program.

Q7B. Please provide:

A signed statement that you will withdraw from the market any lots which may fall out of specifications for the bulk drug product.

A7. The requested information was previously provided in the Stability Commitment Letter. Firm provides an additional copy on page 15 (see points 3, 6, and 7).

Q8. Please clarify whether the same specifications are employed for the finished bulk product at release and at the end of expiration dating, especially regarding degradants.

A8. Firm states that stability specifications are identical to specifications which are used at the time of initial release. These specifications are listed on page 9; acceptable.

Q9. We note from the submitted stability data report that there is no analysis of degradation products. Please explain why the protocol for stability testing requirements listed on page 128 is not being followed.

A9. Firm states that degradation testing is performed on all stability samples. Since no decomposition products have been detected to date during the course of stability studies, the Fujian Institute has failed to incorporate any mention of the test being performed in their stability reports. A "certification" letter stating that all future stability reports will include degradation information is enclosed on page 18.

Q10. The submitted stability data indicate that your product does not meet the current USP requirement on potency. Please re-evaluate your analytical method (the current on page 26 of your Amendment dated December 20, 1996 should be employed). It is recommended that you manufacture new exhibit batches and submit all performance data to demonstrate the new product meets compendial standards. Please include all information regarding the modifications in manufacturing processes, if any.

A10. Starting in 1995, three separate fermentation batches, that have been processed through the (page 58 of 9/15/93 submission), have been combined prior to This combining of and resulted in a larger batch sizes and finished material which assays at approximately 99.0% when calculated on the dried basis. This increase in assay values has resulted from a "cleaner" and has also resulted in a loss of product yield. To date, only two USP batches have been manufactured under AADA 64-104 (#960201 and #951201). The RT stability data (up to 6 months) provided for this two batches on page 20 are acceptable.

Comments:

Since this is a first generic product, and Firm uses different microorganism to produce the drug substance, we need to scrutinize this drug product more carefully. Request Firm to manufacture another batch to meet the 3 batch requirement, and ask Firm to submit additional available stability data from the two other batches. Sample validation pending Firm's third batch (performance data of the new batch needed to be reviewed first).

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable (MAJOR)

19. REVIEWER: Maria C. Shih

DATE COMPLETED: 10/22/96

AADA 64-104

Fujian Institute of Microbiology
U.S. Agent: Chemwerth, Inc.
Attention: David R. Loomis
85 Rimmon Road
Woodbridge, CT 06525

Dear Sir:

This is in reference to your abbreviated antibiotic drug application dated September 15, 1993, submitted pursuant to Section 507 of the Food, Drug, and Cosmetic Act, for Cyclosporine USP (non-sterile bulk).

Reference is also made to your amendments dated January 7, and March 31, 1994.

The application is deficient and, therefore, not approvable under Section 507 of the Act for the following reasons:

> Please note that the official definition of the antibiotic Cyclosporine listed in 21 CFR § 430.4(a)(51) reads "Cyclosporine is a specific cyclic polypeptide consisting of 11 amino acids produced by the growth of *Cylindrocarpon lucidum* Booth or *Tolypocladium inflatum* Gams." The drug substance which you have produced by the growth of *Fusarium solani* therefore does not meet the official definition. The application has not received a comprehensive review for this reason.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

C. Greg Guyer, Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:
AADA 64-104
DUP/Division File
HFD-600/RF
FIELD COPY

Endorsements:
HFD-643/EDuffy/
HFD-643/JHarrison/7/22/94
HFD-617/MAnderson/7/25/94
X:FIM64.104
B:64104.RV1
F/T by mw/7/25/94
NOT APPROVABLE: MAJOR

1. CHEMIST'S REVIEW NO. 1

2. AADA # 64-104

3. NAME AND ADDRESS OF APPLICANT
Fujian Institute of Microbiology
19 Jinbu Road
Chang Shan District
Fuzhou, Fujian Province
PRC

US Agent:
Chemwerth, Inc.
Attention: David R. Loomis
85 Rimmon Road
Woodbridge, CT 06525
(203) 387-7794

4. LEGAL BASIS for ANDA SUBMISSION
21 CFR § 448.23

5. SUPPLEMENT(s)
N/A

6. NAME OF DRUG
Cyclosporine USP (non-sterile bulk)

7. NONPROPRIETARY NAME
Cyclosporine USP (non-sterile bulk)

8. SUPPLEMENT(s) PROVIDE(s) FOR
N/A

9. AMENDMENTS AND OTHER DATES
9/15/93 - original submission
10/12/93 - refuse to file
1/7/94 - amendment
1/28/94 - refuse to file
3/31/94 - amendment
4/20/94 - accepted for filing

10. PHARMACOLOGICAL CATEGORY
Antibiotic

11. HOW DISPENSED
R

12. RELATED IND/NDA/DMF(s)
None cited.

13. DOSAGE FORM
Bulk

14. POTENCY

15. CHEMICAL NAME AND STRUCTURE
Cyclosporine

16. RECORDS AND REPORTS

17. COMMENTS
The bacterial strain used for fermentation is *Fusarium solani* 4-11 [S-42-150-2] and mutated at the Fujian Institute of Microbiology. The definition of the antibiotic listed in 21 CFR § 430.4(a)(51) is the polypeptide produced from *Cylindrocarpon lucidum* Booth, or *Tolypocladium inflatum* Gams. The drug substance is therefore unacceptable due to non-conformance with the monograph.

Deficiency

Please note that the official definition of the antibiotic Cyclosporine listed in 21 CFR § 430.4(a)(51) reads "Cyclosporine is a specific cyclic polypeptide consisting of 11 amino acids produced by the growth of *Cylindrocarpon lucidum* Booth or *Tolypocladium inflatum* Gams." The drug substance which you have produced by the growth of *Fusarium solani* therefore does not meet the official definition.

18. CONCLUSIONS AND RECOMMENDATIONS

RECOMMENDATION - NOT APPROVABLE - MAJOR

19. REVIEWER
Eric P. Duffy, Ph.D.

DATE COMPLETED
7/22/94

AADA 64-104

1994

ChemWerth, Inc.
Agent for: Fujian Institute of Microbiology
Attention: David R. Loomis
85 Rimmon Road
Woodbridge, CT 06525

Dear Sir:

We acknowledge the receipt of your abbreviated antibiotic application submitted pursuant to Section 507 of the Federal Food, Drug and Cosmetic Act for the following:

NAME OF DRUG: Cyclosporine, USP (non-sterile bulk)

DATE OF APPLICATION: September 15, 1993

DATE OF RECEIPT: September 15, 1993

DATE ACCEPTABLE FOR FILING: April 1, 1994

Reference is also made to your amendments dated January 7, 1994, and March 31, 1994 submitted in response to our "Refuse to File" letters dated October 12, 1993, and January 28, 1994, respectively.

We will correspond with you further after we have completed the review of your application.

Please be advised that during the AADA approval process, samples of the active and inactive ingredients, and the AADA exhibit batch(es) may be collected by the FDA district office staff and tested by FDA district or headquarters laboratory staff. Drug substance standards and manufacturer's documentation of the impurity profile should be made available. In addition, batch records, certificates of analysis and specifications and tests for the drug substance, drug product and inactive ingredients may be collected.

Please refer to the Office of Generic Drugs, Policy and Procedure Guide # 35-92 for the number of batches and the batch size requirements for AADA's submitted for the drug substance and drug product.

The subject product of an AADA must conform to the current official compendial monograph requirements and be compatible with the test and assay methods described in that monograph. You must submit adequate documentation and laboratory data in your AADA that prove that any non-official alternate procedures that you choose to use for the analytical control (release) of your product are equivalent to the official compendial procedures. If this information is not submitted, the review of the application will be delayed.

Please identify any communications concerning this application with the number shown above.

Sincerely yours,

Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: AADA#64-104
DUP Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett
HFD-473/JGraham

Endorsements: HFD-615/GJohnston Chief_____date
HFD-615/PRickman, CSO_____date
HFD-615/WRussell, CSO_____date
HFD-643/JHarrison,Chem Branch, Chief_____date
WP File\B:\russell\64-104a
F/T by hrw 4-6-94
AADA ACKNOWLEDGEMENT LETTER!

AADA 64-104

ChemWerth, Inc.
Agent for: Fujian Institute of Microbiology
Attention: David R. Loomis
85 Rimmon Road
Woodbridge, CT 06525

Dear Sir:

Please refer to your Abbreviated Antibiotic Application (AADA) submitted under Section 507 of the Federal Food, Drug and Cosmetic Act for Cyclosporine, USP (non-sterile bulk).

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this AADA under 21 CFR 314.101(d)(3) for the following reason:

> You have failed to provide a master production batch record for at least the largest batch intended for production. You must cite the intended production batch size and list the quantities of components to be used in the batch on the master production batch record.

Thus, it will be not be filed as an abbreviated antibiotic application within the meaning of Section 507 of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell, R.Ph.
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

AADA 64-104
cc: DUP /Jacket
DUP/Division File
HFD-82
HFD-File
Field copy
HFD-600/Reading File
HFD-615/MBennett

Endorsements: HFD-615/Gordon Johnston, Chief date
HFD-PRickman, CSO date
HFD-615/WRussell,CSO date
HFD-643/JHarrison
WP File\russell\64-104
F/T bcw/1-21-94
AADA Refuse to File!

AADA 64-104

ChemWerth, Inc.
Agent for: Fujian Institute of Microbiology
Attention: David R. Loomis
85 Rimmon Road
Woodbridge, CT 06525

Dear Sir:

Please refer to your abbreviated antibiotic application (AADA) submitted pursuant to Section 507 of the Federal Food, Drug and Cosmetic Act for Cyclosporine USP, (non-sterile bulk).

We have given your AADA a preliminary review, and we find that it is not sufficiently complete to merit substantive review. Thus, it will not be filed as an abbreviated antibiotic application within the meaning of Section 507 of the Act.

We are refusing to file this AADA under 21 CFR 314.101(d)(3) for the following reasons:

You have failed to provide an English translation for the certificates of analysis on pages 228 and 257 of the application.

You have failed to provide information regarding the container/closure system used to package your drug substance. Please refer to the Office of Generic Drugs Policy and Procedures Guide 30-91.

You have failed to provide the packaging and labeling section for the batch records provided.

You have failed to provide a master production batch record for at least the largest size batch intended for production.

Please note that approval cannot be given for more than a ten fold scale up from the exhibit batch.

In addition, you must provide four copies of the draft labeling in your archival copy of the application. You have provided one copy. Please submit three additional copies of the draft labeling for the archival copy. In future submissions please provide four copies of the draft labeling in both the archival and review copies.

Within 30 days of the date of this letter, you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell, R.Ph.
Consumer Safety Officer
(301) 295-8315

Sincerely yours,

Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #64-104
DUP/Division File
HFD-600/Reading File
HFC-130/JAllen
Endorsements:
HFD-632/GJohnston
HFD-632/WRickman
HFD-635/JHarrison/Random V
bcw/10-6-93/64-104.ref
F/T by bcw/10-6-93
refuse to file